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(54) Dosage form for pre-menopausal women

(57) Hormonal replacement therapy and contraception is provided by a dosage form of an estrogen selected from 0.5–2.0 mg. of 17β-estradiol, 0.008–0.030 mg. of ethinyl estradiol, and 0.015–0.060 mg. of mestranol; and a progestogen selected from 0.025–0.100 mg. of levonorgestrel, 0.010–0.070 mg. of gestodene, 0.025–0.100 mg. of desogestrel, 0.025–0.100 mg. of 3-ketodesogestrel, and 0.085–0.35 mg. of norethindrone, administered for 23–25 days beginning at day one of the menstrual cycle, followed by 2–5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

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SPECIFICATION

Combination dosage form for pre-menopausal women

The subject invention provides hormonal replacement therapy and contraceptive protection for the pre-menopausal woman in need thereof. Such therapy and contraceptive protection is provided by a combination dosage form of the invention which comprises a low dose of an estrogen combined with a very low dose of a progestogen. A preferred combination dosage form of the invention comprises 0.5–2.0 mg. of 17β-estradiol and 0.025–0.100 mg. of levonorgestrel. The combination dosage form of the invention is administered for the first 23–26 days of the menstrual cycle, followed by 2–5 pill-free or blank pill days, for a total of 28 days in the administration cycle. The preferred administration cycle is 24 days of the combination dosage form and 4 days of no dosage form.

Pre-menopause is defined as the time around 40 years of age when a woman can reasonably be said to be approaching menopause (the last menstrual period) or the time when a woman feels the approach of menopause by experiencing pre-menopausal irregularities in her menstrual cycle or other hypoestrogenic symptoms.

The woman over forty is in a transitional period in which her hormone levels are waning; she still ovulates and yet she experiences many of the symptoms of the hypoestrogenic woman, insomnia, hot flushes, irritability, etc. The fact that these women are still menstruating has led to the uniformed attitude that her complaints are psychosomatic in origin.

The climacteric is marked by many changes due to the natural aging process; all of which are modified by individual life-styles. Both natural and surgical menopause appear to be associated with adverse changes in metabolic parameters and in hormone levels. For example, the metabolic change in the blood lipid profile of the post-menopausal woman may lead to the development of atherscleresis, hypertension and coronary heart disease. See Notelovitz M, Graig SK, Rappaport V, et al; "Menopausal status associated with increased inhibition of blood coagulation," Am J Obstet Gynecol 141:149, (1981); Notelovitz M, Greig HBW, "Natural estrogen and antithrombin III activity in postmenopausal women," J Reprod Med 16:87 (1976); Nielsen FH, Honore E, Kristoffersen K, et al, "Changes in serum lipids during treatment with norgestrel, estradiol-valerate and cycloprogynon.[R] Acta Obstet Gynecol Scand 56:367 (1977) and Paterson MEL, Sturdee DW, Moore B, "The effect of various regimens of hormone therapy on serum cholesterol and triglyceride concentrations in postmenopausal women," By J Obstet Gynecol 87:552 (1980). Adverse changes in hormonal levels of the postmenopausal woman are associated with endometrial and breast cancer and with osterporosis. See Gambrell RD Jr, Bagnell CA, Greenblatt RB, "Role of estrogens and progesterone in the etiology and prevention of endometrial cancer: Review," Am J Obstet Gynecol 146:696 (1983); Gambrell RD Jr, "The prevention of endometrial cancer in postmenopausal women with progestogen,". Maturitas 1:107 (1978); and Nachtigall LE, Nachtigall RH, Nachtigall RD, et al, "Estrogen replacement therapy: I. A 10-year prospective study in the relationship to osteoporosis," Obstet Gynecol 53:277, (1979).

The years after 40 witness an ever increasing number of anovulatory cycles, leaving a woman still menstruating but exposed to variable periods of unopposed estrogen. It is impossible to predict which cycles will be ovulatory or anovulatory because of the absence of any consistent pattern. Thus, the pre-menopausal woman also needs constant contraceptive protection. If one considers the mortality rate in the aging woman due to late childbirth, this contraceptive need becomes of paramount importance. Therefore, in consideration of the appropriate hormone therapy for the pre-menopausal woman, attention must be focused on the effects of such therapy on metabolic parameters as well as on reproductive target organs. In the pre-menopausal woman it is necessary that such therapy also be contraceptive.

In a first aspect, this invention provides a method of providing hormonal replacement therapy and contraception for a pre-menopausal woman, which comprises administering to a pre-menopausal woman in need thereof a combination dosage form of an estrogen selected from

0.5–2.0 mg. of 17β-estradiol,
0.008–0.030 mg. of ethinyl estradiol, and
0.015–0.060 mg. of mestranol;

and a progestogen selected from

0.025–0.100 mg. of levonorgestrel,
0.010–0.70 mg. of gestodene,
0.025–0.100 mg. of desogestrel,
0.025–0.100 mg. of 3-ketodesogestrel, and
0.085–0.35 mg. of norethindrone,

said combination dosage form being administered for 23–26 days beginning at day one of the menstrual cycle, followed by 2–5 pill-free or blank pill days, for a total of 28 days in the adminsitration cycle.

In a second aspect, this invention provides a combination dosage form for hormonal replacement therapy and contraception for a pre-menopausal woman, comprising a combination of an estrogen selected from

0.5–2.0 mg. of 17β-estradiol
0.008–0.030 mg. of ethinyl estradiol, and
0.015–0.060 mg. of mestranol;

and a progestogen selected from

0.025–0.100 mg. of levonorgestrel,
0.010–0.070 mg. of gestodene,
0.025–0.100 mg. of desogestrel, and
0.025–0.100 mg. of 3-ketodesogestrel, and
0.085–0.35 mg. of norethindrone,

said combination dosage form being administered for 23 – 26 days beginning at day one of the menstrual cycle, followed by 2–5 pill–free or blank pill days, for a total of 28 days in the administration cycle.

In the third aspect the invention provides the use of a composition comprising an estrogen selected from

0.5–2.0 mg. of 17β–estradiol
0.008–0.030 mg. of ethinyl estradiol, and
0.015–0.060 mg. of mestanol;

and a progestogen selected from

0.025–0.100 mg. of levonorgestrel,
0.010–0.070 mg. of gestodene,
0.025–0.100 mg. of desogestrel,
0.025–0.100 mg. of 3–ketodesogestrel, and
0.085–0.35 mg of norethindrone,

for the manufacture of a dosage form for providing hormonal replacement therapy and contraception for a pre-menopausal woman by administration of the dosage form for 23 to 26 days beginning at day one of the menstrual cycle, followed by 2 to 5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

A fourth aspect of the invention provides a pack for providing hormonal replacement therapy and contraception for a pre-menopausal woman which pack comprises 23–26 dosage forms each comprising an estrogen selected from

(a) 0.5–2.0 mg. of 17β-estradiol
0.008–0.030 mg. of ethinyl estradiol, and
0.015–0.060 mg. of mestranol;

and a progestogen selected from

0.025–0.100 mg. of levonorgestrel,
0.010–0.70 mg. of gestodene,
0.025–0.100 mg. of desogestrel,
0.025–0.100 mg. of 3-ketodesogestrel, and
0.085–0.35 mg. of norethindrone

(b) 2 to 5 blank pills or other indications to indicate that the daily administration of the 23 to 26 dosage forms should be followed by 2 to 5 pill free or blank pill days.

For all aspects of the invention the preferred estrogen is 17β-estradiol and the preferred progestogen is levonorgestrel. For all aspects of the invention a preferred dosage range of the estrogen component is:

0.75–1.50 mg. of 17β-estradiol,
0.012–0.025 mg. of ethinyl estradiol, and

0.025–0.050 mg. of mestranol; and

a preferred dosage range of the progestogen component is:

0.035–0.085 mg. of levonorgestrel,
0.015–0.060 mg. of gestodene,
0.035–0.085 mg. of desogestrel,
0.035–0.085 mg. of 3-ketodesogestrel, and
0.010–0.30 mg. of norethindrone.

For all aspects of the invention the preferred estrogens are 17β-estradiol, ethinyl estradiol and mestranol; and the preferred progestogens are levonorgestrel, gestodene, desogestrel and 3-ketodesogestrel. 17β-estradiol and levonorgestrel are particular preferrred. Gestodene is also a particularly preferred progestogen. A particularly preferred combination dosage form for all aspects of the invention is a combination in which the estrogen is in a dose of 1 mg. of 17β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel. A further particularly preferred combination dosage form for both aspects of the invention is a combination in which the estrogen is in a dose of 1 mg. of 17β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel, or 3-ketodesogestrel. A preferred course of administration for all aspects of the invention is administration of the combination dosage form of the invention for the first 24 days of the menstrual cycle and no dosage form (i.e. pill-free) or a blank dosage form for the last 4 days of the menstrual cycle. A further preferred course of administration for all aspects of the invention is administration of the combination dosage form for the first 23 days of the menstrual cycle and no dosage form (i.e. pill-free) or a blank dosage form for the last 5 days of the menstrual cycle. The preferred doses equivalent to 1 mg. of 17β-estradiol are, approximately: ethinyl estradiol 0.015 mg. and mestranol 0.030 mg. The preferred doses equivalent to 0.050 mg. of levonorgestrel are approximately: gestodene 0.035 mg., desogestrel and 3-ketodesogestrel 0.050 mg., and norethindrone 0.175 mg. The preferred doses equivalent to 0.075 mg. of levonorgestrel are, approximately: gestodene 0.052 mg., desogestrel and 3-ketodesogestrel 0.075 mg., and norehindrone 0.25 mg. Such equivalent doses may vary depending upon the physiological effect desired and the assay method used.

An especially preferred method of the invention comprises administering to a pre-menopausal woman in need thereof a combination dosage form of 1 mg. of 17β-estradiol and 0.050 mg. of levonorgestrel or 1 mg. of 17β-estradiol and 0.075 mg. of levonorgestrel for 23–26 days beginning at day one of the menstrual cycle, followed by 2–5 pill-free or blank-pill days, for a total of 28 days in the administration cycle. An especially preferred combination dosage form of the invention for providing hormonal replacement therapy and contraception for a pre-menopausal woman comprises a combination dosage form of 1 mg. of 17β-estradiol and 0.050 mg. of levonorgestrel or 1 mg. of 17β-estradiol and 0.075 mg. of levonorgestrel, said combination dosage form being administered for 23–26 days beginning at day one of the menstrual cycle, followed by 2–5 pill-free or blank-pill days, for a total of 28 days in the administration cycle. For all aspects of the invention, the preferred cycle of administration is administration of the combination dosage form for the first 24 days of the menstrual cycle and administration of no dosage form or a blank dosage form for the last 4 days of the menstrual cycle. Or, administration of the combination dosage form for the first 23 days of the menstrual cycle and no dosage form or a blank dosage form for the last 5 days is also preferred. A preferred dose of ethinyl estradiol equivalent to the preferred dose of 1 mg. of 17β-estradiol is 0.015 mg. The equivalent preferred dose of mestranol is 0.030 mg. The preferred equivalent doses of desogestrael and 3-ketodesogestrel which are equivalent to the preferred doses of levonorgestrel, namely, 0.050 mg. and 0.075 mg. are also 0.050 mg. and 0.075 mg. The equivalent preferred doses of gestodene to 0.050 mg. and and 0.075 mg. of levonorgestrel are 0.035 mg. and 0.052 mg.

It is to be understood that in this specification and the accompanying claims norgestrel may be used in place of levonorgestrel, but at twice the stated dose of levonorgestrel. The accompanying claims should be construed accordingly. Norgestrel is a racemic compound while levonorgestrel is one of the optically active isomers. Levonorgestrel is particularly preferred.

The progestogen levonorgestrel is well known and has been marketed in oral contraceptive formulations (at doses of 0.15 mg. and higher) for many years. Its chemical name is (-)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one. Norgestrel's common name is 17α-ethynyl-18-homo-19-nortestosterone. Gestodene, deogestrel, and 3-ketodesogestrel are newer progestogens in various stages of clinical development and use. The new compound, gestodene, differs from norgestrel by a double bond in the 15 position and is progestationally active per se, whereas desogestrel is believed to be inactive as the parent molecule and is though to undergo two

metabolic steps for progestational activity. Desogestrel is believed to be metabolized first to the biologically active 3β-hydroxydesogestrel with estrogenic/androgenic activity and then to 3-ketodesogestrel, which has progestogenic activity; it differs from norgestrel by a methylene group at position 11. Norethindrone's chemical name is 17-hydroxy-19-norpregn-4-en-20-yn-3-one. It is also known as 19-norethisterone or norethisterone. Norethindrone acetate may be used in place of norethindrone, and hence the term "norethindrone" in the accompanying claims is to be understood as referring to either the free alcohol or its acetate.

17β-estradiol is the most potent naturally occurring estrogen in mammals. Its chemical name is estra-1,3,5(10)-triene-3,17-diol. 17β-estradiol (or β-estradiol) is its common name. Ethinyl estradiol and mestranol are both synthetic estrogens which have an ethinyl group at the 17 position of the estradiol ring structure. Mestranol additionally has a methoxy group rather than a hydroxy group at the 3 position of the estradiol ring structure. Ethinyl estradiol and mestranol are used in oral contraceptive-formulations. The composition of such marketed oral contraceptives is shown in Table 15–2 on page 454 in Chapter 15 "Fertility Control and its Complications" by Bruce R. Carr and James E. Griffin in *Williams Textbook of Endocrinology,* seventh edition, (Jean D. Wilson M.D. and Daniel W. Foster M.D. (W. B. Saunders Company, Philadelphia, 1985).

An example of a pack which may be used in the fourth aspect of the invention or for providing the dosage forms for use by the patient in other aspects of the invention is a blister pack type product as is commonly used with oral contraceptive products. Such product would normally comprise the appropriate number of dosage tablets in a sealed blister pack in a cardboard, paperboard or plastic sleeve with a protective cover or box. Each combination dosage tablet blister container may be numbered or otherwise marked for the first 23–26 days of the menstrual cycle, [as, for example, prescribed by the patient's physician]. The remaining 2–5 (pill-free) days of the 28 day administration cycle would contain blank-pills or unfilled blisters or other marking devices to assist the patient in following the prescribed administration cycle. The combination estrogen and progestogen dosage form of the invention is preferably provided as a tablet, caplet or capsule in a manner known in the art. Similarly a blank pill is preferably a tablet, caplet or capsule containing no active hormonal agents. Other oral or parenteral dosage preparations or packages may be provided as known in the art.

CLAIMS

1. The use of a composition comprising an estrogen selected from

0.5–2.0 mg. of 17β-estradiol
0.008–0.030 mg. of ethinyl estradiol, and
0.015–0.060 mg. of mestranol;

and a progestogen selected from

0.025–0.100 mg. of levonorgestrel,
0.010–0.070 mg. of gestodene,
0.025–0.100 mg. of desogestrel,
0.025–0.100 mg. of 3-ketodesogestrel, and
0.085–0.35 mg. of norethindrone,

for the manufacture of a dosage form for providing hormonal replacement therapy and contraception for a pre-menopausal woman by administration of the dosage form for 23 to 26 days beginning at day one of the menstrual cycle, followed by 2 to 5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

2. The use as claimed in Claim 1 in which the estrogen is 17β-estradiol.

3. The use as claimed in Claim 1 or 2 in which the progestogen is levonorgestrel.

4. The use as claimed in Claim 1 or 2 in which the progestogen is gestodene, desogestrel or 3-ketodesogestrel.

5. The use as claimed in Claim 1 in which the dosage form comprises an estrogen selected from:

0.75–1.50 mg. of 17β-estradiol,
0.012–0.025 mg. of ethinyl estradiol, and
0.025–0.050 mg. of mestranol; and

and a progestrogen selected from:

0.035–0.085 mg. of levonorgestrel,
0.015–0.060 mg. of gestodene,
0.035–0.085 mg. of desogestrel,

0.035–0.085 mg. of 3-ketodesogestrel, and
0.10–0.30 mg of norethindrone.

6. The use as claimed in Claim 1 in which the estrogen is in a dose of 1 mg. of 17β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

7. The use as claimed in Claim 1 in which the estrogen is in a dose of 1 mg. of 17β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. or levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

8. A pack for providing a hormonal replacement therapy and contraception for a pre-menopausal woman which pack comprises
(a) 23 to 26 dosage forms each comprising an estrogen selected from:

0.5–2.0 mg. of 17β-estradiol
0.008–0.030 mg. of ethinyl estradiol, and
0.015–0.060 mg. of mestranol;

and a progestogen selected from

0.025–0.100 mg. of levonorgestrel,
0.010–0.070 mg. of gestodene,
0.025–0.100 mg. of desogestrel, and
0.025–0.100 mg. of 3-ketodesogestrel, and
0.085–0.35 mg. of norethindrone

and
(b) 2 to 5 blank pills or other indications to indicate that the daily administration of the 23 to 26 dosage forms should be followed by 2 to 5 pill free or blank pill days.

9. A pack as claimed in Claim 8 in which the estrogen selected is 17β-estradiol.

10. A pack as claimed in Claim 8 or 9 in which the progestogen selected is levonorgestrel.

11. A pack as claimed in Claim 8 in which the estrogen is selected from:

0.75–1.50 mg. of 17β-estradiol,
0.012–0.025 mg. of ethinyl estradiol, and
0.025–0.050 mg. of mestranol; and

the progestogen is selected from

0.035–0.085 mg. of levonorgestrel,
0.015–0.060 mg. of gestodene,
0.035–0.085 mg. of desogestrel,
0.035–0.085 mg. of 3-ketodesogestrel, and
0.10–0.30 mg. of norethindrone.

12. A pack as claimed in Claim 8 in which the estrogen is in a dose of 1 mg. of 17β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

13. A pack as claimed in Claim 8 in which the estrogen is in a dose of 1 mg. of 17β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

14. A pack as claimed in any one of Claims 8 to 13 which comprises 24 dosage forms and 4 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 4 days of the menstrual cycle.

15. A pack as claimed in any one of Claims 8 to 13 which comprises 23 dosage forms and 5 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 5 days of the menstrual cycle.

16. A pack according to Claim 8 comprising 24 dosage forms each comprising 1 mg. of 17β-estradiol and 0.50 mg. or 0.075 mg. levonorgestrel and 4 blank pills or other indications to incidate that no dosage form or a blank pill is administered for the last 4 days of the menstrual cycle.

17. A pack according to Claim 8 comprising 23 dosage forms each comprising 1 mg. of

17β-estradiol and 0.50 mg. or 0.075 mg. of levonorgestrel and 5 blank pills or other indicates to indicate that no dosage form or a blank pill is administered for the last 5 days of the menstrual cycle.

18. A pack for providing a hormonal replacement therapy and contraception for a pre-monopausal woman substantially as hereinbefore described.

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